REVIEW

CME CREDIT

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Epidural steroids for back and leg pain: Mechanism of action and efficacy

ABSTRACT

Epidural injections of glucocorticoids may help some patients with back and leg pain. The efficacy of this therapy has not been conclusively proved; however, when weighed against the risks, cost, and outcomes of spinal surgery, epidural glucocorticoids are a reasonable alternative in selected patients whose back and leg pain is functionally limiting. We review the rationale, available data, techniques, and indications for these injections.

KEY POINTS

Mechanical compression may be the initial event leading to numbness and weakness, but inflammation often is the cause of radicular pain.

Epidural injections of a combination of a local anesthetic and a glucocorticoid can reduce pain and improve function for patients with radicular pain due to disc herniation, spinal stenosis, or neuritis and for some patients with back pain.

Effective use of epidural glucocorticoid therapy depends on proper patient selection, appropriate expectations, and proper injection technique.

The transforaminal approach for epidural injection is gaining popularity and offers some advantages over traditional approaches for properly selected patients.

MOST PATIENTS with acute back and leg pain get better over time. The big problem is controlling pain and maintaining function until the patient recovers naturally. When recovery is slow and pain severe, patients and physicians may seek an invasive solution, ie, spinal surgery.

Epidural glucocorticoid injections are commonly given to relieve pain and improve mobility without surgery, buying time for healing to occur. These injections have a good theoretical rationale, but they do not help every patient and do not reliably change the long-term outcome of the underlying back problem.

Who then should receive epidural glucocorticoid injections? And what kind of benefit can they reasonably expect?

CAUSES OF SCIATICA

Compression is not the whole story

In 1948, Lindblom and Rexed[1] first proposed that pressure on the spinal nerve, caused by a disc fragment or bone spur, is the primary cause of sciatic pain in patients with lumbar disc herniation.

Nerve root compression probably is not the only factor contributing to radicular symptoms, however. For one thing, compression does not always produce pain: roughly 40% of people with no history of sciatic pain have disc protrusion or herniation on postmortem examination.[2] Myelographic abnormalities can be found in as many as 35% of people without symptoms,[3] and abnormalities on magnetic resonance imaging (MRI) in as many as 60%.[4]

Furthermore, surgical decompression does not relieve symptoms in every case. While

surgery may provide more rapid improvement than nonoperative care, most patients do well without it.[5] Patients with acute sciatic symptoms typically recover in 2 to 6 weeks, long before the extruded disc material is reabsorbed and the pressure on the affected nerve is relieved. And some patients with sciatic pain have no evidence of frank nerve root compression on MRI. Something more is at work here.

Inflammation: The additional factor

In many patients, the additional factor is inflammation.

Although acute compression of the nerve root often causes weakness and numbness, radicular pain is usually not the first symptom. This is where inflammation comes in. Normal nerves respond to nondestructive pressure by loss of function—they stop transmitting normal signals. Not until inflammation sets in does the nerve begin sending painful signals to the brain, either spontaneously or in response to normally benign stimuli.[6]

Inflammation in the injured disc, facet capsule, epidural tissues surrounding the nerve root, and the nerve root itself dramatically increases the nerve's sensitivity to stimuli. Once inflammation is present, the nerve becomes exquisitely sensitive to pressure, producing prolonged, pain-generating discharges with either gentle manipulation or pressure.[7]

Up to 40% of symptom-free people have disc herniation

Observations of inflammation

In 1950, Lindahl and Rexed[8] first noted inflammation, edema, and proliferative or degenerative changes in biopsy samples from posterior nerve roots of patients undergoing laminectomy.

Berg,[9] using myelography, noted that swollen nerve roots consistently shrank as the sciatic symptoms abated.

Green[10] observed similar findings in a patient treated with intramuscular dexamethasone, suggesting that the inflammatory component of sciatica might be as important as the root compression.

Saal et al[11] demonstrated an immunocompetent cellular reaction in acute human disc herniations. They identified aggregates of macrophages and T lymphocytes at the interface of herniated nuclear material and the epidural space and noted that this reaction decreased in patients over time from symptom onset.

Inflammatory and neurochemical mediators

Current theories of sciatic pain consider inflammatory and neurochemical mediators as principal modulators, if not precipitators, of radicular symptoms.

Phospholipase A_2, an inflammatory mediator, regulates free arachidonic acid and eicosanoid production[12] and plays a role in a variety of musculoskeletal conditions. Levels are elevated in the serum and synovium of patients with rheumatoid arthritis,[13,14] and high levels have also been found in the human intervertebral disc. Phospholipase A_2 may play a role in painful disc disease and may have humoral effects on local and remote neural tissues.[15]

Pain-related neuropeptides. Fine nerve endings in the outer layers of the annulus connect with a plexus of nerves running cranial and caudal through the posterior longitudinal ligament. Stimulation or disruption of these nerves is thought to produce back pain, and perhaps referred, but not radicular, leg pain.[16,17]

Disruption of the annulus may result in proliferation of these fine endings in the zone of injury and ingrowth of granulation tissue and nerve endings into deeper layers of the annulus. Discogenic symptoms may ensue: localized, severe back pain, particularly worse with sitting, flexion, extension, and exercise.[18] Pain-related neuropeptides such as substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide may be released and then "leak" from the nucleus through the annulus.

Increased local concentrations of these neuropeptides are thought to sensitize the free nerve endings, generating painful discharges, and producing back pain. It is also likely that these neuropeptides sensitize the adjacent nerve root and dorsal root ganglion, generating nerve root symptoms.[19] Hence, pain-related neuropeptides may play a role, through slightly different mechanisms, in both back and radicular pain.

GLUCOCORTICOID ACTIONS

Glucocorticoids directly or indirectly inhibit the synthesis or release of a number of inflammatory substances, including phospholipase

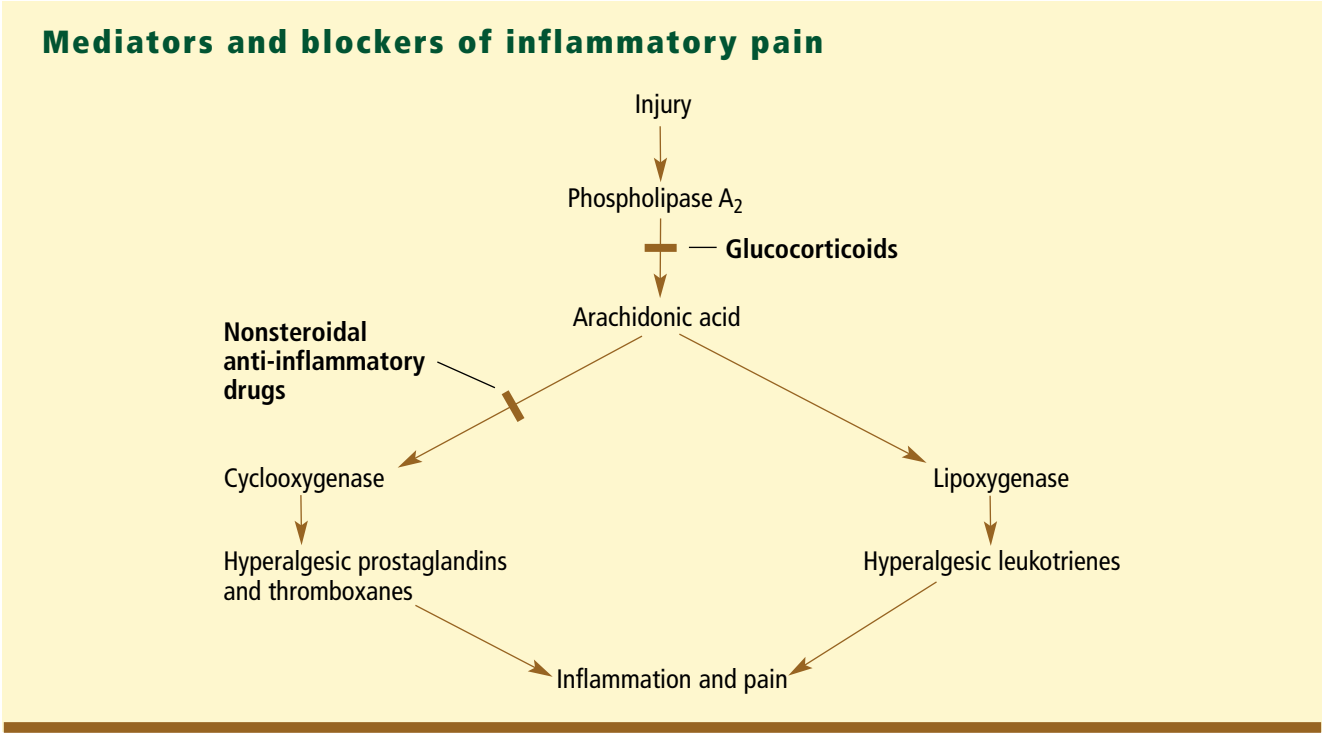


FIGURE 1

A_2, arachidonic acid and its metabolites,[20] tumor necrosis factor alpha, interleukin 1, and prostaglandin E_2.

Glucocorticoids also may make the endothelium less "sticky" to resting polymorphonuclear leukocytes.[21] Leukocytes disrupt endothelial membranes as they adhere to and then penetrate the vascular wall. This damage may cause an increase in capillary permeability and lead, subsequently, to tissue edema.[13] Damaged endothelial cells also release a variety of cytokines, some of which attract monocytes and activated macrophages. Once engaged in the local inflammatory process, these mononuclear phagocytes may elaborate a variety of inflammatory substances[14] that directly stimulate local and regional nociceptive nerve endings.

Thus, in radiculopathy, glucocorticoids ameliorate both the early phenomena of inflammation (edema, fibrin deposition, capillary dilatation, leukocyte aggregation and phagocytosis) and late effects (capillary and fibroblast proliferation, collagen deposition, cicatrization).

Whether epidural glucocorticoid injections relieve back pain is more speculative than whether they relieve radicular pain, and most studies in patients with back pain showed uneven responses. There is a potential mechanism for benefit, however: the posterior longitudinal ligament, along with the outer annulus of the intervertebral disc, is richly innervated with nociceptive free nerve endings. Distortion or inflammation of these structures could contribute to the symptom of referred back pain seen in many patients with degenerative disc disease. Reduction in impulses from these nerves could reduce the back pain component in some patients with back and leg pain.

Glucocorticoids act higher in the inflammation cascade than NSAIDs do

NSAID failure does not preclude glucocorticoid use

The glucocorticoids exert their action higher in the inflammatory cascade than do the nonsteroidal anti-inflammatory drugs (NSAIDs). While NSAIDs inhibit prostaglandin and thromboxane production by inhibiting the cyclooxygenase pathway, they have no effect on leukotrienes produced via the lipoxygenase pathway. Glucocorticoids, on the other hand, inhibit the arachidonic acid pathway that provides precursors for both cyclooxygenase and lipoxygenase synthesis (FIGURE 1).

Furthermore, injecting the glucocorticoid into the immediate vicinity of the inflammation provides an effective dosage many times higher than can be obtained with systemic medications.

Hence, failure of NSAIDs to relieve radicular pain does not preclude the use of glucocorticoids.

HISTORY OF EPIDURAL GLUCOCORTICOID USE

In the 1920s, Viner[22] injected large volumes of saline and procaine into the lumbar epidural space to treat back pain and lumbar radiculopathy.

In 1960, Brown[23] reported complete transient relief in four patients with sciatica lasting 6 to 24 months treated with methylprednisolone. The same year, Goebert et al[24] gave three injections of procaine and hydrocortisone to 239 patients with sciatica, and reported greater than 60% relief of symptoms in 58% of patients.

Techniques and indications are evolving

Most studies of steroid injections had methodologic flaws

Since that time, techniques and indications for this therapy have been changing constantly.

A variety of anesthetics have been used (procaine, lidocaine, bupivacaine), as well as a number of glucocorticoids (hydrocortisone, methylprednisolone, triamcinolone). Physicians have tried saline alone, anesthetics alone, glucocorticoids alone, and combinations of each. Dosages of each medication and the number and timing of injections have varied widely.

Both caudal and lumbar interlaminar approaches have been used to reach the epidural space.[25] Intrathecal injections were popular for a time, but the risk of arachnoiditis caused by either the glucocorticoid or its carrier substance[26] and the less common occurrence of meningitis (aseptic, septic, cryptococcal, or tuberculous) have made this approach uncommon in modern pain management.

Different physicians have advocated epidural glucocorticoid therapy for acute and chronic pain, for back or leg pain, and for diagnoses ranging from acute herniated nucleus pulposus to end-stage degenerative disc disease and spinal stenosis.

Epidural injections are usually prescribed along with a number of other "conservative" treatments, which have ranged from prolonged bed rest and lumbar traction to passive and active physical therapy; therapeutic heat, cold, and ultrasound; and a variety of anti-inflammatory medications. Although physical therapy in some form is usually included, the type and duration have never been standardized.

CLINICAL EFFECTIVENESS OF GLUCOCORTICOID INJECTIONS

Proving that glucocorticoid injections are effective has been difficult. Most clinical studies of this therapy have suffered from one or more flaws:

- Lack of appropriate controls
- Lax treatment protocols, introducing a variety of concurrent therapies along with the epidural glucocorticoid treatments
- Failure to standardize the treatment, even in a single study, with respect to glucocorticoid type, dose, delivery method, and inclusion of local anesthetics
- Failure to design randomized, prospective, or blinded studies
- Lack of uniform outcome measures, and few objective measures.[27] Clinical trials that used different outcome measures have come to different conclusions.[28]

Uncontrolled studies

Uncontrolled studies abound.[29–31]

In one retrospective study that included patients with a variety of symptoms and diagnoses, the addition of methylprednisolone to epidural infusions provided superior results in patients with chronic pain, and fewer "valueless" results in patients with recurrent pain.[25]

In a series of 161 patients with disc herniation,[32] 12% had excellent results and 46% had fair results when given injections of prednisolone 20 mg. This therapy failed in 25%, who subsequently underwent surgery.

Andersen and Mosdal[33] reported that 10 of 17 patients treated with methylprednisolone and lidocaine felt significantly better at first, but only one patient experienced substantial long-term benefit.

Berman et al,[34] in a retrospective study of

367 patients with leg pain, also noted that outcomes deteriorated over time, but 60% of patients still reported good to excellent results 1 year after treatment.

Power et al[35] declared epidural glucocorticoids an unmitigated failure and felt it unethical to continue their study after none of their 16 patients benefitted from injections of bupivacaine and methylprednisolone. Although 10 patients had some initial relief at 24 hours to 3 months, none avoided surgery.

Controlled studies

The results of the few well-controlled studies have varied as well. The most reliable studies suggest that glucocorticoid injections provide significant benefits to some patients with primarily radicular symptoms, but the benefit is of limited duration, and the effect is harder to demonstrate over time. Glucocorticoids appear to speed return to function and allow patients to reduce their medication doses and increase their activity.

Dilke et al[36] found glucocorticoids effective in a controlled, randomized, double-blind trial in 100 consecutive patients treated for unilateral sciatica. Patients received methylprednisolone 80 mg via the lumbar epidural route, while controls received a placebo injection of saline. The treatment and control groups were comparable with respect to age, sex, neurologic deficit, symptoms, symptom duration, and occupational demands. Treated patients used significantly less analgesic medication, had a higher return-to-work rate, a lower rate of surgery, and greater subjective pain relief initially and at 3 months.

In contrast, Snoek et al[37] found no difference in outcomes between treated and control patients in a double-blind study of 51 patients treated for lumbar root compression of variable duration. The two groups were comparable, and compression was confirmed by myelography, but outcomes were assessed at only 24 to 48 hours after injection (glucocorticoid response may not be maximal for up to 6 days), and long-term follow-up consisted of a late chart review to see which patients had subsequently required surgery. The treated group experienced greater improvement in sagittal motion, sciatic stretch, motor weakness, and back, radicular, and impulse pain and needed fewer analgesics, but the differences were not statistically significant. Likewise, though more of the treated patients felt improved (67% vs 42%), and the physiotherapists assessed more of the treated patients as improved (70% vs 43%), these differences did not reach statistical significance.

Most recent randomized, controlled studies have shown a marginal benefit from glucocorticoid therapy, at best. Ridley et al[38] found a significant initial improvement in treated patients in a randomized trial in 39 patients, but there was no residual benefit at 6 months. Klenerman et al[39] found that 75% of patients with acute sciatica had satisfactory improvement regardless of whether they had injections of saline, methylprednisolone, or bupivacaine.

Bush and Hillier,[40] in a double-blind, controlled study of caudal epidural injections, found triamcinolone significantly superior to placebo, but again, the primary benefit was seen early on. At 4 weeks the treated group reported significantly greater pain relief and mobility compared with patients receiving placebo (75% improved vs 18% improved on placebo). At 1 year the treated patients showed greater improvement than placebo patients (83% improved vs 63% improved on placebo), but only the increase in straight leg-raising tolerance was significant.

Most recent studies showed a marginal benefit from steroid injection, at best

Watts and Silagy[41] performed a meta-analysis of 11 randomized studies with 907 patients and noted that the benefits of epidural glucocorticoid injections for lumbar radiculopathy diminished over time.

Carette et al[42] found that epidural injections of methylprednisolone, compared with saline injections, afforded mild-to-moderate improvement in leg pain, mobility, and sensory deficits and reduced the need for analgesics during the first 6 weeks after treatment. The injections had no effect on the need for subsequent surgery, however. The treatment effect diminished after 2 to 3 months.

Hopwood and Abram[43] found that symptoms in just over half of 212 patients treated with lumbar epidural glucocorticoid injections were significantly improved 2 weeks after treatment. At 6 months and 12 months, patients who had a good response initially had improved even more.

REASONS FOR TREATMENT FAILURE

Considering the inconsistent findings of these studies, surprisingly little has been said about factors predisposing to treatment failure.

Patient characteristics influence outcomes in epidural glucocorticoid therapy just as they do in any other aspect of low back pain care. Issues of secondary gain may also impair recovery in these patients just as they do in surgical patients.

Jamison et al[44] identified five factors that predicted a poor outcome with epidural glucocorticoid therapy:

- Greater number of previous treatments for pain
- Greater dependence on pain medications
- Pain not increased with activity
- Pain increased by cough
- Unemployment.

Hopwood and Abram[43] found an increased risk of treatment failure among patients with:

- Chronic pain (lasting > 6 months)
- Nonradicular pain
- Unemployment due to back pain
- History of smoking.

Needle placement may be incorrect in up to 25% of cases

Inability to place the medication where it is needed may also lead to treatment failure. Fluoroscopy has demonstrated that needle placement in caudal injections is either dorsal to the sacrum or intravenous in as many as 25% of cases.[45] Renfrew et al[46] noted that, without fluoroscopy, even experienced physicians get the needle into the epidural space in only 60% of cases.

Moreover, despite the use of larger volumes of solution in the caudal approach or the delivery of medications closer to the target tissue with the lumbar approach, there is still no guarantee that glucocorticoids delivered dorsally will reach the ventral epidural space, where most of the putative pain generators reside.

Possible ineffectiveness of glucocorticoids. Our understanding of the causes of radicular and referred pain remains the weak link in establishing the role of epidural glucocorticoids, or any injectable or topical medicine for that matter, in treating acute or chronic nerve root pain. The variable efficacy of glucocorticoids in some patients with back and leg pain may be due to an inherent inability of corticosteroids to affect some pain-producing pathways.

WHEN TO RECOMMEND EPIDURAL INJECTIONS

Concrete guidelines are difficult to establish, as back and leg pain disorders are highly variable.

Not the first line of treatment

Epidural glucocorticoids should be incorporated into a general program of back care and are rarely the first line of treatment.

With any benign back problem, initial care should include a short period of rest (reduced activity but not bed rest), ice to the painful area, and NSAIDs. After the acute phase (1–2 weeks), management must include physical therapy to restore mobility and back strength, aerobic exercise for back fitness and weight loss, and lifestyle changes, including diet programs, smoking cessation, and activity modification.

Indications, contraindications

For the most part, epidural glucocorticoid therapy should be reserved for patients with symptoms of radiculopathy. Even then, patients with radicular symptoms due to spinal stenosis are less likely to benefit than are those with disc herniation.[47]

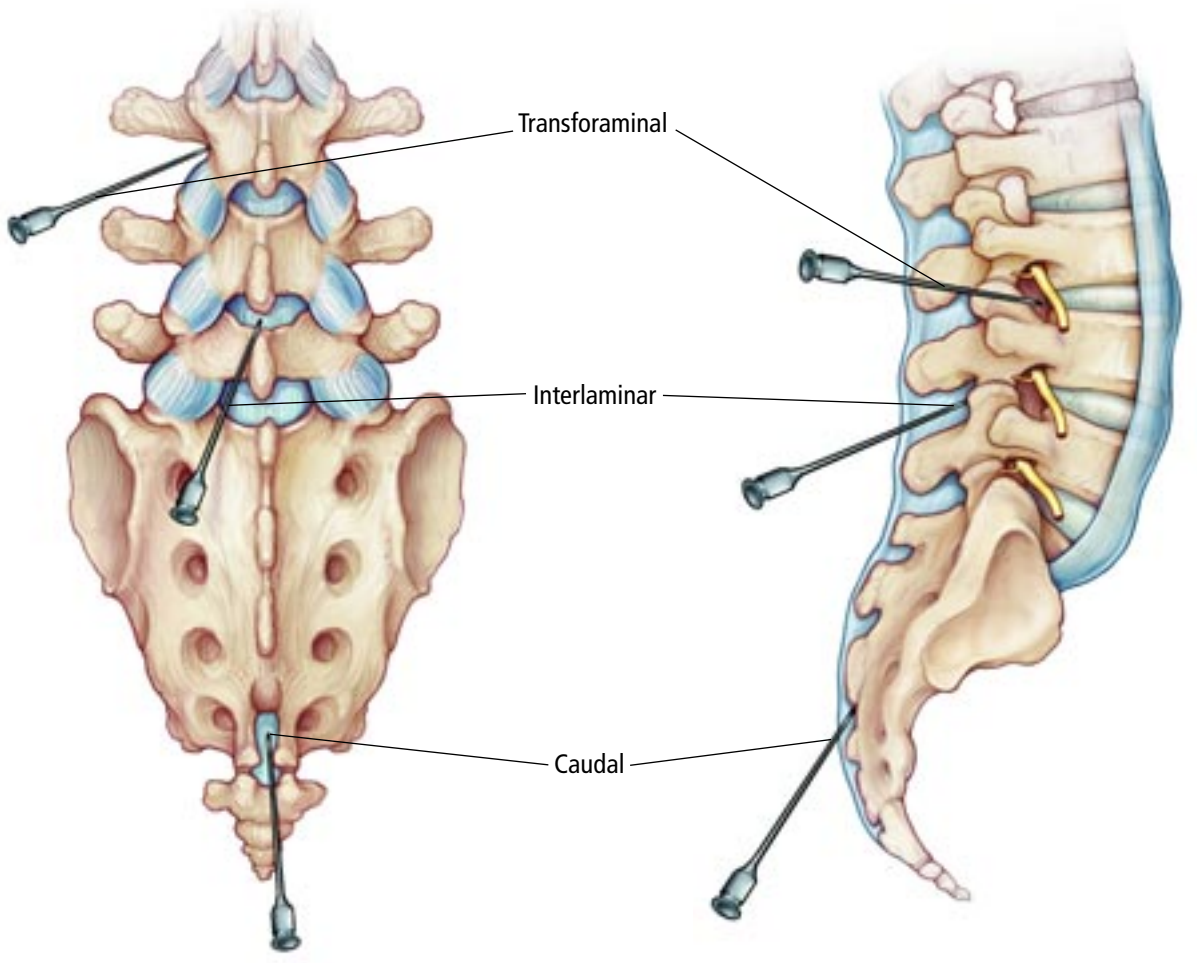
Randomized, controlled trials are needed to prove which patients are most likely to benefit from epidural glucocorticoids, and when and for how long. When weighed against the risks, cost, and outcomes of spinal surgery, however, epidural glucocorticoids provide a reasonable alternative in selected patients whose back and leg pain is functionally limiting.

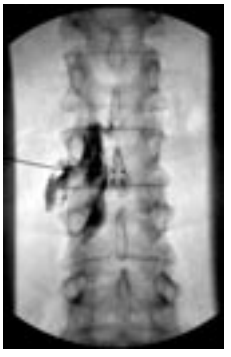
General indications for epidural glucocorticoid treatment include:

- Radicular pain and paresthesias persisting more than 4 to 6 weeks despite appropriate nonoperative therapy
- Back pain associated with prominent leg pain
- Failure to respond to rest, NSAIDs, and initial physical therapy
- Physical findings of nerve root irritation or compression—positive straight-leg raising test, radicular pain pattern, minimal motor deficit

Routes of epidural glucocorticoid injection

Epidural injections of glucocorticoids have traditionally been given through either a caudal or interlaminar route; the newer transforaminal route has proven highly effective in experienced hands.





For any epidural injection, fluoroscopic guidance is recommended. Here, transforaminal epidural dye injection confirms proper placement.
Note, with correct placement, the spread of the dye to the epidural space and the recess and sleeve of the nerve route.

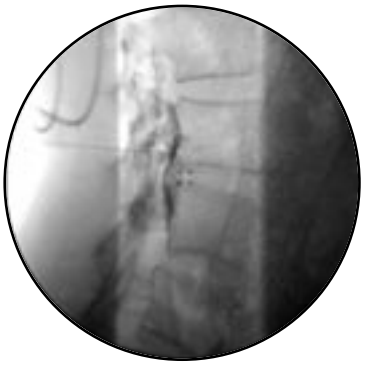


FIGURE 2

- Physical findings of spinal stenosis—polyradicular pain associated with standing and walking and relieved by sitting.

Contraindications to epidural glucocorticoid injection include:

- Ongoing use of anticoagulant medications
- Any evidence of local infection or diskitis (diabetes mellitus also increases the risk of infectious complications and is a relative contraindication to this therapy)
- Prominent motor deficit or paresis suggestive of severe root or cauda equina compression
- Failure of previous injections to provide benefit
- Imaging studies demonstrating severe spinal stenosis.

PROPER TECHNIQUE

Regimens vary from center to center, but some basic principles apply:

Fluoroscopy is recommended

Injections are rarely the first line of treatment

The procedure is technically demanding. Inaccurate needle placement reduces the chance of treatment success and increases the risks of potentially serious complications. Some practitioners can place the needle blindly, but accidental intrathecal injection can lead to complications such as meningitis or adhesive arachnoiditis.[48]

In any but the most experienced hands, the needle should be inserted under fluoroscopy, using radiographic contrast to document an epidural, extravascular placement before injecting medications.[46] This precaution will greatly improve glucocorticoid delivery while reducing risks.

Three-injection regimen

Glucocorticoids can be injected by themselves or with a local anesthetic or saline diluent.[29,36] The local anesthetic may relieve acute pain and muscle spasm and can, through the extent of neural blockade, indicate whether the needle is placed correctly.

There are no data to suggest that any one glucocorticoid is better than another. Usual dosages include methylprednisolone 80 mg or triamcinolone 50 to 80 mg.

Large volumes of saline are not necessary, and may cause complications: 6 mL is enough to disperse radiocontrast from the level of the sacrum up to L1.[30] A 10.0-mL infiltration of a glucocorticoid and saline, or a glucocorticoid with bupivacaine 0.25% or lidocaine 0.5% should be sufficient for any application.

A typical course of therapy consists of three injections. Usually, a single injection of a local anesthetic and glucocorticoid is given, followed in 3 to 4 weeks by a second injection (as the benefit of any single injection may not be apparent for up to 7 days). If relief is only partial, the patient receives a third injection, but if excellent and persistent relief is obtained from two injections, the third injection is not given. The patient should not be given more than one course per year.

Which route?

Glucocorticoids should be injected into the epidural space, with care to avoid unintentional intrathecal injection. Either a caudal or interlaminar lumbar approach can be used, depending on the practitioner's preference and experience (FIGURE 2). The transforaminal approach has been gaining wide acceptance for treating unilateral radiculopathy (see below).

The interlaminar approach, in which the needle is placed in the upper lumbar region in a seated patient, was first described by Brown[49] in 1977. He reported excellent results, with no complications, in a small series. This method requires smaller volumes to be injected to reach the target tissue than with the caudal approach.

The caudal approach, on the other hand, is thought by some to be less demanding and entails much less risk of intradural injection.

TRANSFORAMINAL EPIDURAL INJECTION

In the transforaminal approach, a smaller-gauge blunt needle is inserted into the epidural space via the intervertebral foramen.[50] The procedure is done with the patient prone and with fluoroscopic guidance, which helps to prevent damage to the nerve root.[51]

This technique allows the glucocorticoid to be placed very close to the irritated nerve root—much closer than with the interlaminar

approach—and allows one to use lower doses. It is particularly useful in large disk herniations, foraminal stenosis, and lateral disk herniations. Radiation exposure is minimal in experienced hands.

Complications of transforaminal injections

Technical complications common to both the interlaminar and the transforaminal approach are rare, but include headaches due to dural puncture, infections, intravascular injection, hematoma, arachnoiditis, unintentional subarachnoid and subdural injection, local discomfort, and vasovagal reaction to the needle.

Glucocorticoid complications may include suppression of the hypothalamic-pituitary axis, elevation of blood sugar, elevation of blood pressure, and fluid retention. Also, there is an ever-present risk of allergic reaction to one of the medications.

There is a higher chance of damaging a nerve root with the transforaminal approach than with the interlaminar approach. Using a blunt, pencil-point, or curved needle may reduce the risk of this complication.

It is very important to keep talking with the patient during the procedure. If significant radicular pain is triggered during placement of the epidural needle or injection of the medication, the physician should stop the procedure immediately and check the position of the needle and the source of pain.

Irrespective of the approach, patients should be observed for evidence of medication reaction or spinal blockade. The physician should also discuss the possibility of postinjection headache (1%–5%), increased radicular symptoms (1%), and risks of persistent spinal headaches or infection requiring treatment.

Outcomes of transforaminal injections

In several reports,[50–52] long-term success rates for transforaminal epidural glucocorticoid injection ranged from 71% to 84%. The average number of injections was 1.8. Patients with disc herniations and radiculopathy attained maximal improvement in 6 weeks. Generally, patients who obtained little relief from the first injection got little benefit from a second or third injection. And while 50% to 75% of patients with radicular pain received temporary relief after epidural injections, only 25% to 57% received excellent long-term relief.

Interestingly, transforaminal injections seem to have predictive value in deciding whether a patient might benefit from surgery. Studies show that most patients who obtain substantial leg pain relief from selective nerve root blocks, even if temporary, will benefit from surgery for the radicular pain when the nerve root injury is associated with a disc herniation or lateral bony stenosis. Conversely, 95% of patients who get no relief from injections also do not benefit from surgery for chronic radiculopathy.[52]

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